* NOTICES *

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] the preparation approach of the drug content polymer micell constituent which does not include the polymer micell which more specifically condensed this invention mutually substantially about the polymer micell system containing a water poorly soluble drug, and ** -- it is related with a constituent [like].
[0002]
[Description of the Prior Art] The system which enclosed the drug into liposome or a polymer micell is known in order to raise the bioavailability of a water poorly soluble or hydrophobic drug. Application to an extensive drug is possible for the approach of enclosing a drug into the micell of this polymer through interactions including the hydrophobic bonding ability of a hydrophobic polymer segment and a drug using the block copolymer which has a hydrophilic polymer segment and a hydrophobic polymer segment, and it is [among these] especially interesting from the ability to offer a submicron, very small drug content polymer micell moreover.
[0003] the block copolymer in which some this invention persons have a polyoxyethylene segment, and he has the Polly alpha-amino-acid segment as a hydrophobic polymer segment as a hydrophilic polymer segment is useful as support for drug support suitable for enclosure of a hydrophobic drug -- finding out -- ** -- the drug content polymer micell which enclosed a variety of drugs into the polymer micell formed from support itself and them was offered (for example, refer to JP,6-107565,A or a U.S. Pat. No. 5,449,513 specification). [like] ** -- a hydrophobic drug with the fixed support [like] for drug support, and the point which can enclose efficiently an anticancer agent, adriamycin (doxorubicin), a daunomycin (daunorubicin), methotrexate, mitomycin-C, etc. especially -- attention -- ********.
[0004] However, when, enclosing a water poorly soluble drug which does not dissolve in water substantially irrespective of fluctuation of pH etc. into the polymer micell of the above-mentioned support for drug support for example, unlike adriamycin with solubility increasing to acid water, it may condense or meet between drug content micells, and the drug content polymer micell of the magnitude made into the purpose may be unable to be prepared efficiently.
[0005]
[Problem(s) to be Solved by the Invention] Therefore, the purpose of this invention is further with a means given in above-mentioned JP,6-107565,A and other advanced-technology reference to offer not only the hydrophobic drug that can be enclosed somewhat good but the means which can also enclose an insoluble damage-at-sea nature drug into a polymer micell efficiently substantially in water.
[0006]
[Means for Solving the Problem] this invention persons use the polymer micell formation nature block copolymers or those qualification polymers of itself known. for example, KRN5500 (a 6-[4-deoxy-4-[(E [2], 4E) - tetra-DEKAJI enoyl glycyl] amino-L-glycero-beta-L-MANNO hept pyranosyl] amino-9H-pudding -- that is) which is poorly soluble at water farther than the above-mentioned adriamycin etc. When the sonication process was subsequently carried out, it found out the process in which a polymer

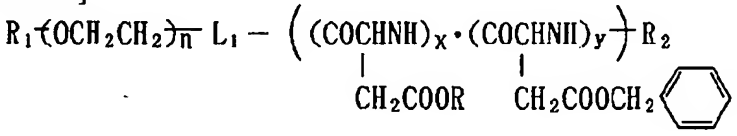
micell is made to form the semisynthesis derivative which has the fatty-acid chain of Spica mycin (spicamycin) in a specific organic solvent, and that a desired drug content polymer micell could be offered efficiently. Moreover, it also found this invention persons that qualification of this block copolymer can control the enclosure yield and polymer micell size to the inside of the polymer micell of a drug. It found out that the above operation effectiveness was acquired even when it applies to a water poorly soluble (as [call / still / although it is not damage-at-sea nature about 5500 KRN / it / water poor solubility or hydrophobicity]) drug like KRN5500 which was able to be enclosed with the polymer micell somewhat efficiently by the conventional approach, without being substantially limited to the thing of water-insoluble nature further again.

[0007] According to this invention, a water poorly soluble drug is the preparation approach of the drug content polymer micell constituent which mainly exists in the core of the polymer micell of the block copolymer which has a hydrophilic polymer segment and a hydrophobic polymer segment. Therefore, in (A) water miscibility organic solvent The block copolymer which has a polyoxyethylene segment as a hydrophilic polymer segment, and a water poorly soluble drug are mixed. (B) By dialyzing the obtained mixture in water through permeable membrane, a drug content polymer micell is formed and the preparation approach of the drug content polymer micell constituent characterized by what a solution or dispersion liquid including (C) this drug content polymer micell is ultrasonicated for is offered.

[0008] the following formula (I) among the block copolymers which have a polyoxyethylene segment as the above-mentioned hydrophilic polymer segment -- or (II) --

[0009]

[Formula 3]



(I)

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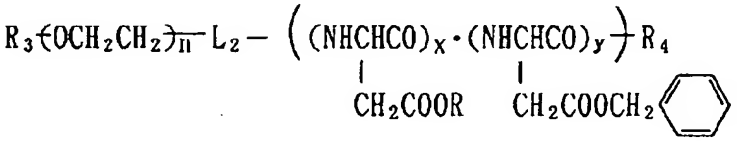


(II)

[0010] The inside R1 and R3 of [above-mentioned each type expresses a hydrogen atom or a low-grade alkyl group, respectively. R2 expresses C1 - 29 aliphatic-series carbonyl group, or the aryl carbonyl group of a hydrogen atom, saturation, or partial saturation. R4 expresses C1 - 30 aliphatic-series oxy-radical of a hydroxyl group, saturation, or partial saturation, or an aryl-low-grade alkyloxy radical. L1 The connection radical chosen from the group which consists of NH-, -O-, and -OCO-Z-NH- (here, Z is C1 - 4 alkylene groups) is expressed. - L2 The connection radical of OCO-Z-CO- and -NHCO-Z-CO- (here, Z is C1 - 4 alkylene groups) is expressed. - R C1 - 30 aliphatic-series radical of a hydrogen atom, saturation, or partial saturation are expressed, and n is the integer of 4-2500. x and y Are the integer from which it differs and those sum totals are set to 2-300, and the same or the unit which attached x and y When both those units exist, the block copolymer expressed with] which exists in random, respectively, or can form a block and can exist can be used suitable for especially the above-mentioned preparation approach. In this way, it is without the drug content polymer micell in which it is prepared and deals is substantially accompanied by what was condensed mutually (though contained). Consist only of a drug content polymer micell which it is to a maximum of 10%, or as a drug since it is physically [have efficiently the drug chosen from the group which consists of KRN5500, taxol, camptothecin, and those water poorly soluble derivatives in the polymer micell, and] stable -- ** -- offer of a constituent including a drug content polymer micell [like] also becomes possible. therefore, ** -- the constituent [like] itself is offered as another mode of this invention.

[0011]

[Detailed Description of the Invention] The block copolymer which can be used for the preparation approach of this invention is a block copolymer which has a polyoxyethylene segment as a hydrophilic polymer segment, and includes any polymers which can attain the purpose (that is, the drug content polymer micell constituent which has a desired property for a water poorly soluble drug according to the preparation approach of this invention can be offered) of this invention. Although not limited, the block copolymer expressed with the above-mentioned formula (I) or (II) is made into the start, and, specifically, it is included by the block copolymer which also says what is indicated by above-mentioned JP,6-107565,A, and a thing which is indicated by the U.S. Pat. No. 5,698,529 specification which consists of a polyoxyethylene segment and a polypropyleneoxy segment to this invention. In addition, the word of the "polymer segment" or prefix "Pori" used on these specifications is used with the concept which includes the mind of oligomer or oligo, as long as the purpose of this invention is met.

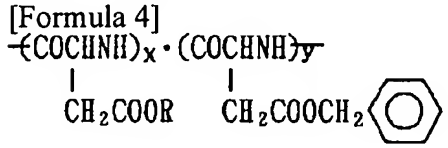
[0012] ** -- the damage-at-sea nature drug enclosed into a polymer micell using a block copolymer [like] By enclosing into this polymer micell, any drugs which can raise the bioavailability (bioavailability) of a drug are included. what is limited by drug effect like the antitumor agent mentioned later -- it is not -- moreover, a steroid (an example --) It is not limited by the class of compounds, such as the water poor solubility of alkaloid (an example, vincristine, vinblastine, colchicine, etc.), such as cortisone and a testosterone, peptides (an example, an insulin, calcitonin, etc.), and others, or a hydrophobic compound,, either. However, the thing for which submicron one and the drug content polymer micell which has the diameter of dozens of nm - hundreds of nm more concretely can be prepared efficiently according to the above-mentioned preparation approach, The polymer micell of magnitude [like / a row] can avoid nephrogenic discharge and the nonspecific prehension by reticuloendothelium cell lineage. L.W.Seymour et al., J.Biomed.Mater.Res., and 21 (1987) -- [for example,] 1341-1358, D.C.Litzinger et al., Biochim.Biophys.Acta, 1190, 99 -107 (1994) reference, and a certain block copolymer in which a polyoxyethylene segment forms the shell of a polymer micell can send a drug to a solid tumor site by high selectivity. (For example, G.S.Kwon et al., J.Contr.Rel., 29 (1994) 17 -23 reference) If it takes that it is possible etc. into consideration, a water poorly soluble or hydrophobic anticancer drug can be especially mentioned as a suitable thing as the above-mentioned drug. ** -- as an anticancer drug [like], although not limited, these water poorly soluble derivatives, such as adriamycin, a daunomycin, methotrexate, mitomycin-C, KRN5500, taxol (taxol), and camptothecin (camptothecin:4-ethyl -4 - hydroxy-1H-[3', 4':6, 7] in DORIJINO [1, and 2-PIRANO b] quinoline-3 and 14 [4H and 12H]] dione), are mentioned. Especially the drug that can be used with sufficient convenience by the preparation approach of this invention can mention KRN5500 and taxol which were not necessarily able to prepare a drug content polymer micell constituent efficiently, and camptothecin in a conventional method.

[0013] The constituent said to this invention includes any constituents containing a drug content polymer micell, and means a liquefied object or a freeze-drying object etc. which usually includes saccharides, such as an aquosity medium (for example, sterilized water, a physiological saline) containing this polymer micell, or a lactose. These constituents can prepare the polymer micell acquired by the preparation approach of this invention by the formula of itself known using an excipient, a diluent, etc. which are regularly used by preparation of physic pharmaceutical preparation by the case.

[0014] Although the water miscibility organic solvent which can be used by the preparation approach of this invention may change the optimal thing according to the class of drug enclosed with a polymer micell, they are polar solvents, such as the organic solvent which can distribute the above-mentioned block copolymer and a drug to the dissolution thru/or homogeneity, for example, dimethylformamide, (DMF), dimethyl sulfoxide (DMSO), an acetonitrile, and a tetrahydrofuran (THF), at least. Although these solvents may contain water to the range which does not have a bad influence on the solubility of a drug, 50 [for example,], [capacity / capacity %], that [its] to which the following [5 capacity / capacity %] are not adding water desirable still more substantially [water] is more desirable. It means not adding water to the industrial grade or reagent grade of these solvents intentionally, saying "water is not added substantially." Therefore, it is not limited to the solvent "which is not adding water

substantially" being an absolute non-aqueous-solvent system.
[0015] ** -- the above-mentioned block copolymer in the inside of a solvent [like] and mixing of a drug prepare block-copolymer content liquid and drug content liquid separately, respectively, mix them, or to a solvent, coincidence or after adding one by one, they may mix a block copolymer and a drug. Shaking, mechanical agitation, and sonication can perform mixing. Although the suitable content ratio of the drug mixed and a block copolymer may be changed according to the solvent, drug, and block copolymer to be used, the ratio of the drug to a block copolymer is weight criteria, and is usually 5 - 30% especially preferably 5 to 50% preferably 1 to 300%. although the drug in mixed liquor and the concentration of a block copolymer can be the concentration which they are used and may exist in the state of [homogeneous] the dissolution in a solvent -- usually -- a block copolymer -- 0.01-40 (weight/capacity) % -- desirable -- 0.05-25(weight/capacity) % -- it is 0.1-10(weight/capacity) % especially preferably. Although mixed processing may be what kind of temperature as long as it is temperature to which mixed liquor is liquid and does not carry out inactivation of the drug, -5 degrees C - 60 degrees C of mixed liquor usually perform it in near a room temperature (15-25 degrees C) over the time amount which will be in a homogeneous condition preferably.
[0016] In this way, subsequently the prepared mixed liquor is dialyzed to water through permeable membrane. Permeable membrane will not be limited by the magnitude of the quality of the material and pore etc. if efficiently separable from the raw material which had the formed drug content polymer micell used, a solvent, a drug, a block copolymer, etc. However, it is usually equal to the molecular weight of the block copolymer used, or it is desirable to use the permeable membrane of the cellulose system which has the separation (cut-off) ability of larger molecular weight than it. As for this processing, it is desirable under the above-mentioned mixed processing temperature and the same temperature to carry out for at least 5 hours.
[0017] Aquosity dispersion liquid including the drug content polymer micell after the above-mentioned dialysis are applied to sonication next. As for sonication, it is convenient to usually carry out using SONIKETA (sonicator) of the probe type regularly used by crushing of a cell etc. Although it is generally desirable to perform the above-mentioned dispersion liquid under ice-cooling (about 4 degrees C), as long as it is the temperature which does not have a bad influence on a drug content polymer micell, you may be what kind of temperature. Although the processing time is changed with the reinforcement of the acoustic wave to irradiate etc., it chooses the magnitude which the drug content micell which exists in dispersion liquid makes the purpose, and sufficient time amount for the thing in the condition that less than 1 micrometer of average diameters of a micell met between 800nm or less or a micell preferably stopping usually existing. For example, when using the model VC 100 (Sonics & Materials Inc., Connecticut, USA) equipped with standard 6mm probe of probe type SONIKETA, sonication for 1 - 180 minutes is preferably performed in the cycle of standing for 1 second with an acoustic wave exposure for 1 second for several 10 seconds to 12 hours.
[0018] In this way, excluding substantially the meeting (condensation) micell in the condition that the micells which may be formed of dialysis processing met, the drug content polymer micell acquired exists in mixed liquor, after each micell has dissociated independently. Since the micell which exists in these condition of having dissociated is thermodynamically stable, under the usual preservation conditions, it does not form a meeting micell mutually substantially and condensation cannot cause it easily, either. Therefore, the path of a micell can offer the micell mixture which has narrow distribution intentionally.
[0019] as [indicate / the preparation approach of following this invention / as mentioned above, / by for example, the JP,6-107569,A notice] -- "-- warming -- it can distinguish from processing, ultrasonic irradiation processing, or organic solvent processing" clearly, and the operation effectiveness which was not able to be expected is done so from them.
[0020] The block copolymer suitable for especially forming the above-mentioned drug content polymer micell is expressed with the above (I) or (II). The polymer micell constituent which can be obtained by the preparation approach of the above-mentioned drug content polymer using the block copolymer expressed with these formulas (I) or (II(s)) This polymer micell is not meeting or condensing mutually

(). Or it consists only of a thing which has the single core of a micell and which has a globular form mostly, or the description is in drugs being KRN5500, taxol, camptothecin, and those water poorly soluble derivatives, and in itself, in advanced-technology reference, it is non-** and is new.
[0021] Although you may be what kind of thing as long as the block copolymer expressed with a formula (I) and (II) is specified by each formula and it meets this purpose, the optimal thing may be changed according to combination with the drug to be used. For example, probably, what has a long-chain aliphatic series radical in the polymer section equivalent to the core plasticity segment of a polymer micell will be desirable when a drug has a long-chain aliphatic series radical like KRN5500. That is, the enclosure property (for example, compatibility of a drug and the core section) of a drug, the path of a polymer micell, etc. can be controlled by embellishing the polymer section equivalent to this core plasticity segment.
[0022] Therefore, [0023] in a formula (I) and (II)
[Formula 4]



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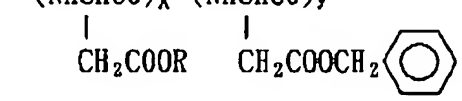


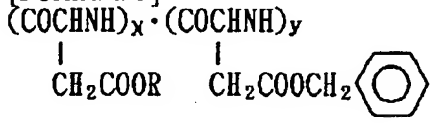
[0024] the section -- either x or y -- not existing (it being an integer 0) -- or both x and y can be positive numbers other than integer 0.
[0025] R in the above-mentioned formula can be C1 - 30 aliphatic-series radical of a hydrogen atom, saturation, or partial saturation according to the drug enclosed with a polymer micell as it mentioned above. As C1 - 30 aliphatic-series radical of saturation, the alkyl group of a straight chain or branching can be mentioned, it is low-grade alkyl groups, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and n-hexyl, or carbon atomic numbers are the inside of the straight chain to 30 [thoria KONCHIRU (or myricyl)], or branching thru/or a high-class alkyl group. As an example of the middle class thru/or a high-class alkyl group, although not limited, octyl, deca nil, lauryl, Millis Chill, cetyl, 14-methyl hexa deca nil, 16-methyl octadecanyl, DOKOSHIRU, tetra-KOSHIRU, hexa KOSHIRU, myricyl, etc. can be mentioned. It uses combining above KRN(s)5500, and when x is except integer 0, as for R, it is desirable that it is except a hydrogen atom and they are a middle class or a high-class alkyl group. Moreover, as an aliphatic series radical of partial saturation, a carbon atomic number is two or more, and can mention DODESERU (C12), FISETERIRU (C14), ZOMARIRU (C16), oleyl (C18) one, KATADONIRU (C20), etc. Explanation of these aliphatic series radicals is common also into the aliphatic series parts of C1 which defines R4 - 30 aliphatic-series oxy-radical. Moreover, phenylmethyl (benzyl), phenylethyl (phenethyl), etc. are mentioned as aryl [which is said to an aryl-low-grade alkyloxy radical] low-grade alkyl.
[0026] R1 and R3 can be a hydrogen atom or a low-grade alkyl group.
[0027] R2 can be a hydrogen atom, an acyl group corresponding to the above C1 - 30 aliphatic-series radical, or an aryl carbonyl group (an example, benzoyl). As a concrete thing of an acyl group, acetyl, a propionyl, an iso propionyl, decanoyl one, DOTEKA noil (RAURIRIRU), tetra-decanoyl (Millis Chill), hexa decanoyl (PAL MICHIRIRU), octadecanoyl, 9, 12-OKUTADE rudder enoyl (Reno Lil), IKOSA noil (ARAKIDONIRU), etc. can be mentioned.
[0028] Generally L1 and L2 are the connection radicals which may change freely by the manufacture approach of a formula (I) and the block copolymer of (II). The polymer whose L1 of a formula (I) is -NH-, -O-, or -OCO-Z-NH- For example, it is the hydroxyl group of omega[after forming a

polyoxyethylene segment by anion-living polymerization]-end The amino group or two -OCO-Z-NH (Z) C1 - 4 alkylene groups -- it is -- after converting, when an alpha-amino-acid chain is expanded through the above-mentioned amino group, it can obtain by the carbon-dioxide elimination polymerization method (the so-called NCA law) using N-carboxylic anhydride of beta-benzyl aspartate. the same -- L1 -- the polymer of -O- a polyoxyethylene segment -- an anion-living polymerization method -- forming -- the omega-end -- a polyamino acid segment -- NCA -- or it makes it elongate by law -- or NCA -- what can be depended on the condensation of the Polly beta-benzyl aspartate separately manufactured by law and a polyoxyethylene can be mentioned.

[0029] After the block copolymer expressed with a formula (II) manufactures a polyoxyethylene and Polly beta-benzyl aspartate according to an individual, it can convert omega-end of a polyoxyethylene into a carboxyl group for them, or can usually mention what can be offered by connecting a carboxyl group and N-end amino group of polyamino acid through that of the alkylene dicarboxylic acid of C 1-6 as occasion demands.

[0030] Moreover, [0031] [in / attached above-mentioned x or y for example, / a formula (I)]

[Formula 5]



[0032] When, as for both a part and the part to which a formula (II) corresponds, x and y exist, they may exist, where random or a block is formed.

[0033] When it exists in the random condition, after forming a Polly beta-benzyl aspartate part, it can provide by carrying out partial hydrolysis of the benzyl, or carrying out the ester interchange of a part of benzyl to other acyl groups. This ester exchange reaction can be performed by processing the block copolymer which has the above-mentioned Polly beta-benzyl aspartate segment in one to C30 alcohol which is equivalent to R under existence of an acid catalyst. the condition of having mixed N-carboxylic anhydride of beta-benzyl aspartate and beta-acyl (except benzyl) aspartate as an exception method -- NCA -- it can also manufacture by enforcing law.

[0034] On the other hand, for example, by the NCA method, where a block is formed, when it exists, after forming the segment of x parts or y part, the target block copolymer can be offered by subsequently forming the segment of y part or x parts. nx and y in the above block copolymers can also be which integer if the block copolymer which can attain the purpose of this invention is offered. However, n is the integer of 4-2500 and is usually 50 to 1500 integer more preferably. On the other hand, although either can be 0, as for x and y, it is desirable that x is 0 in that case. moreover, x and y are the same -- or -- differing -- the sum total -- 2-300 -- it can be the integer of 5-50 preferably. Under the present circumstances, although the ratio of x pair y is very good in what kind of value, it can take the value of 1:7-7:1, for example.

[0035] the thing of the formula (I) from the ease of manufacture among above formulas (I) and block copolymers of (II) -- convenience -- good -- it can be used -- especially -- ** -- combination use of the drug chosen from the group which consists of a block copolymer [like], KRN5500 and taxol, camptothecin, and those damage-at-sea nature induction is desirable. Moreover, R of a formula (I) is a middle class or a high-class aliphatic series radical, and the thing both x and whose y are zero or more positive numbers and the thing whose x is 0, and especially the constituent that comes to contain the drug content polymer micell concerning combination with the above-mentioned drug are desirable. In addition, the above-mentioned damage-at-sea nature derivative includes any derivatives which have the solubility to KRN5500, taxol and camptothecin, and the water approximated mostly.

[0036] In this way, excluding that in which a polymer micell has a diameter 1 micrometers or more, the divisor of 10nm - 800nm has a pitch diameter, and the constituent which comes to contain the drug content polymer micell offered is very stable in the usual condition (for example, condition distributed to the parenteral solution etc.), and the meeting or condensation between micells hardly produces it. moreover, ** -- since the micell of magnitude [like] can avoid the nonspecific prehension by

nephrogenic discharge or reticuloendothelium cell lineage as mentioned above, it can attain the advanced use effectiveness of a drug.

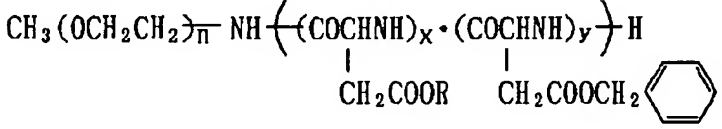
[0037] ** -- although it can be considered as the pharmaceutical preparation for internal use, or the pharmaceutical preparation for parenteral administration according to a drug, the constituent which comes to contain a drug content micell [like] is especially advantageous when considering as the pharmaceutical preparation for parenteral administration. When carrying out to the pharmaceutical preparation for parenteral administration, for example, injections, the compound of a salt and a saccharide, and others is added as occasion demands, the above-mentioned drug content polymer micell is blended into the liquefied diluent regularly used by physic pharmaceutical preparation, for example, water, ethyl alcohol, or propylene glycol, and a suspending agent, for example, ethoxyl-ized isostearyl alcohol, a polyoxyethylene sorbitol, etc. can be further blended and prepared as occasion demands so that it may become isosmotic to blood.

[0038]

[Example] Although an example is given and this invention is explained still more concretely hereafter, it does not mean limiting the range of this invention to these.

[0039] Example 1: manufacture [0040] of a block copolymer

[Formula 6]



(R=H、$C_{16}H_{33}$)

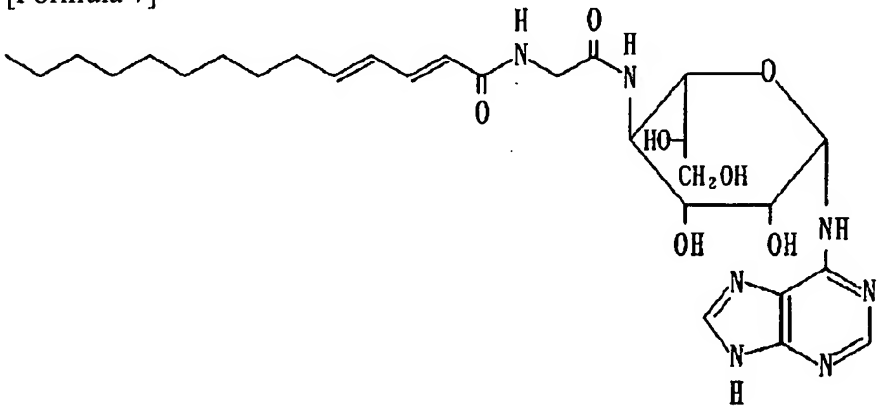
[0041] The example 1 or M.Yokoyama et al. of JP,6-107565,A, Bioconjugate According to the approach of a publication, it manufactures to Chem. and 3 (1992)295-301. By 1 H-NMR measurement of the phenyl proton of the Polly (beta-benzyl L-aspartate) segment (henceforth a PBLA chain), and the methylene proton of the Pori (oxyethylene) segment (henceforth a PEG chain) The molecular weight of a PBLA chain and a PEG chain prepared the block copolymer (henceforth PEG-PBLA) which are about 3,500 and about 12,000, respectively.

[0042] (1) Partial hydrolysis above-mentioned PEG-PBLA (1.00g) was dissolved in chloroform 10ml. Subsequently, 1.5ml (0.43Ns) of NaOH solutions in mixed liquor of water, a methanol, and 2-propanol (capacity factor 1:2:2) was added. the reaction mixture after agitating violently at 0 degree C, adding 200micro of glacial acetic acids l subsequently to the above-mentioned solution and neutralizing for 15 minutes -- diethylether 100ml -- it poured into inside and precipitate was produced. Precipitate was separated and it dissolved in 10ml of distilled water. In this way, 0.6ml (12Ns) of concentrated-hydrochloric-acid water solutions was added to the obtained solution, and, subsequently overnight dialysis was further carried out to distilled water for 3 hours to 0.1NHCl water solutions using spectra pore (Spectrapor) 3 permeable membrane (molecular weight cut-off = 3,500). Subsequently, the polymer in a dialysis bag was freeze-dried and the 0.55g block copolymer [it is also called PEG-P (Asp, BLA) above-mentioned R=H and the following] by which partial hydrolysis was carried out was obtained.

[0043] (2) PEG-PBLA (2.00g), cetyl alcohol (1.06g), and p-toluenesulfonic-acid monohydrate (200mg) were put in into the ester interchange flask by cetyl alcohol, and, subsequently toluene 40ml was added. It heated at 80 degrees C for 24 hours, agitating this solution. reaction mixture -- diethylether 400ml -- it poured into inside. The produced precipitate was washed by diethylether and, subsequently it dried under reduced pressure. In this way, 1.77g [block copolymer / which were partially exchanged by the cetyl group in the benzyl of PEG-PBLA / [it is also called PEG-P (C16, BLA) the above-mentioned R=C16H33 and the following]] was obtained.

[0044] In addition, the content of the BLA unit in PEG-P (Asp, BLA) and PEG-P (C16, BLA) can measure the absorbance of the benzyl alcohol produced by [of the BLA unit of these block copolymers]

carrying out perfect alkali hydrolysis in 257.5nm, and can determine it by contrasting with the benzyl alcohol content of unsettled PEG-PBLA.
[0045] result: -- PEG-P (C16, BLA) which the reduced properties of x and y of the formula (I) of PEG-P (Asp, BLA) obtained by the above (1) are 9.5 and 7.4, respectively, and was obtained by the above (2) -- said -- the reduced properties of x and y were 4.1 and 12.8, respectively.
[0046] Example 2: enclosure (dialysis) of KRN5500 into a polymer micell
KRN5500: [0047]
[Formula 7]



[0048] Dialysis was performed to G.S.Kwon et al., Pharm.Res., and 12 (1995) 192-195 according to the approach of a publication. It will be as follows if summarized. The solution which dissolved each block copolymer in N.N-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) was mixed with the solution which dissolved KRN5500 in those solvents independently, respectively. At the room temperature, mixing was agitated for 10 minutes and performed. Next, overnight dialysis was carried out to distilled water using cellulose permeable membrane (molecular weight cut-off = 12,000-14,000).
[0049] (1) The used block copolymers were above-mentioned PEG-PBLA, PEG-P (Asp, BLA), and PEG-P (C16, BLA). On the other hand, the operating rate of KRN5500 to these block copolymers was adjusted so that it might become 30% on weight criteria. The condition of the survival in the dialysis bag after dialysis was as being shown in the next table 1.
[0050]
[Table 1]
表 1

実験 No.	ブロックコポリマー	(mg)	KRN5500 (mg)	溶媒	状態
1	PEG-PBLA	5.0	1.5	DMF	沈殿
2	PEG-PBLA	5.0	1.5	DMSO	沈殿
3	PEG-P(Asp, BLA)	5.0	1.5	DMF	沈殿
4	PEG-P(Asp, BLA)	5.0	1.5	DMSO	沈殿
5	PEG-P(C_{16}, BLA)	5.0	1.5	DMF	沈殿
6	PEG-P(C_{16}, BLA)	5.0	1.5	DMSO	均質

[0051] The homogeneity liquid of experiment No.6 of Table 1 only showed only few opacity. That is, according to this experiment system, it can be especially regarded as a thing with the remarkably increasing solubility to the water of KRN5500 by the incorporation (or enclosure) of a drug with the sufficient effectiveness to the inside of a polymer micell.
[0052] (2) The operating rate of KRN5500 to a block copolymer was made into 10 % of the weight, and the enclosure experiment by the above-mentioned dialysis was conducted using two sorts of block

copolymers. In addition, the solution was filtered after dialysis by 5C filtration membrane (magnitude of about 1 micrometer of pore), and the mean particle diameter and the disprsion index (dispersion index) of KYUMURANTO were measured by dynamic light scattering. A result is shown in Table 2.

[0053]

[Table 2]

表 2

実験 No.	ブロックコポリマー	溶媒	収率[1] (%)	直径[1] (nm)	分散指数[2] (μ_2/G'^2)
1	PEG-PBLA	DMF	31.2	446	0.27
2	PEG-PBLA	DMSO	53.4	552	0.30
3	PEG-P(C_{16}, BLA)	DMF	5.2	136	0.23
4	PEG-P(C_{16}, BLA)	DMSO	38.7	362	0.32

[0054] 1) It seems that most part of the big particle indicated to be precipitate in Table 1 is removed by the above-mentioned filtration processing which is the value measured after filtration by 5C filtration membrane so that change of transparency may be observed.

[0055] (3) The operating rate of KRN5500 to a block copolymer was made into 5, 10, and 30 % of the weight, and the enclosure trial of a drug was performed using PEG-P (C16, BLA). A result is shown in Table 3.

[0056]

[Table 3]

表 3

実験 No.	KRN5500 (重量%)	溶媒	収率[1] (%)	直径[1] (nm)	分散指数[2] (μ_2/G'^2)
1	5	DMF	66.8	207	0.22
2	5	DMSO	45.1	267	0.28
3[2]	10	DMF	5.2	136	0.23
4[2]	10	DMSO	38.7	362	0.32
5	30	DMF	0.7	115	0.22
6	30	DMSO	9.5	329	0.29

[0057] 1) The example 3 of an experiment same at 5C filtration membrane as measured-value 2 table 2 after filtration : removal of a big particle (sonication)

50ml of KRN5500 enclosure polymer micell content liquid prepared by dialysis processing was prepared on the same conditions as experiment No.4 of Table 3, and it processed in the cycle of standing for ultrasonic irradiation and 1 second for 1 second by 4 degrees C using equipment equipped with standard 6mm probe of the probe type SONIKETA (probetype sonicator) model VC 100 (Sonics & Materials Inc., Connecticut, USA). The result of having ultrasonicated in 60 minutes is shown in drawing 1 . Drawing 1 shows that it falls remarkably with a disprsion index by sonication whose average diameter of KYUMURANTO is 10 minutes. In addition, change was not seen by the transparence liquid obtained by processing, without completely separating KRN5500, also when processing for these 60 minutes is performed.

[0058] The result of having analyzed grain-size distribution of this transparence liquid with the histogram method of mark watt (Marquadt) is shown in (a) of drawing 2 R> 2, and (b). In addition, two peaks are seen according to dispersion distribution on the strength (gamma), the first peak is in 81nm, and the second peak is in 390nm. (The particle 1 micrometers or more was not observed at all.) Although it can consider that the big particle of the second peak is the floc (or meeting object) of the

micell resulting from the diameter of about 200-800nm, the percentage of the particle of the diameter exceeding 100nm is only 8.2 mere% so that it may see from the weight part fraction cloth of (b) of drawing 2 R> 2 (weight-fractioneddistribut ion). This weight fractionation average diameter is 71nm.
[0059] Example 4: the above-mentioned examples 2 and 3 were repeated except having replaced with KRN5500 as a drug and having made the amount of the drug used to this polymer (5.0mg) into 10 % of the weight (0.5mg) using the same block copolymer as the preparation above-mentioned examples 2 and 3 of the drug content polymer micell using camptothecin (Camptothecin). In addition, sonication according to Example 3 was performed using the aliquot of KYUMURANTO obtained according to Example 2. A result is shown in Table 4.
[0060]
[Table 4]
表 4

実験 No.	ポリマー	溶媒	封入された薬物 (μg)	キュムラント平均粒径(nm)	超音波照射後の粒径(nm)
1	PEG-P(C_{16}, BLA)	DMF	52	-	-
2	PEG-P(C16, BLA)	DMSO	157	2399	512
3	PEG-PBLA	DMF	18.5	-	-
4	PEG-PBLA	DMSO	164	4153	386

[0061] In addition, ultrasonic irradiation was performed for 5 minutes, and the amount of camptothecin in permeable membrane was measured with the absorbance in 370nm, and particle size was determined by dynamic light scattering.
[0062] Sonication shows that the particle size of a drug content polymer micell can be reduced intentionally.

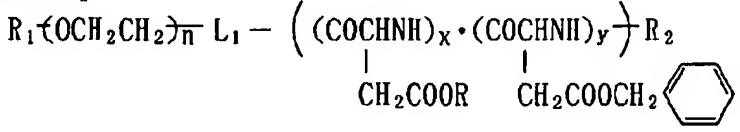
[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

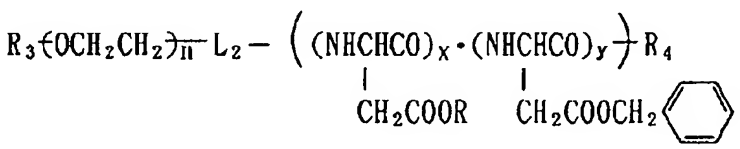
CLAIMS

[Claim(s)]
[Claim 1] It is the preparation approach of a drug content polymer micell constituent that a water poorly soluble drug mainly exists in the core of the polymer micell of the block copolymer which has a hydrophilic polymer segment and a hydrophobic polymer segment. (A) The block copolymer which has a polyoxyethylene segment as a hydrophilic polymer segment, and a water poorly soluble drug are mixed in a water miscibility organic solvent. (B) The preparation approach of the drug content polymer micell constituent which forms a drug content polymer micell and is characterized by what a solution or dispersion liquid including (C) this drug content polymer micell is ultrasonicated for by dialyzing the obtained mixture in water through permeable membrane.
[Claim 2] the block copolymer which has a polyoxyethylene segment -- the following type (I) -- or (II) --
[Formula 1]



(I)

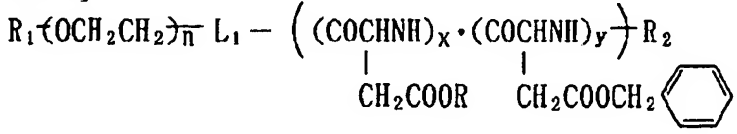
または



(II)

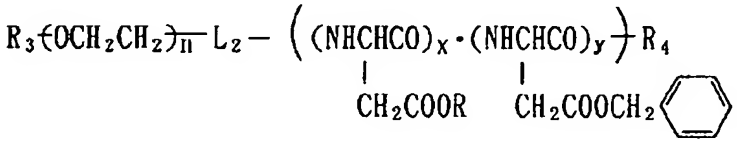
The inside R1 and R3 of [above-mentioned each type expresses a hydrogen atom or a low-grade alkyl group, respectively. R2 expresses C1 - 29 aliphatic-series carbonyl group, or the aryl carbonyl group of a hydrogen atom, saturation, or partial saturation. R4 expresses C1 - 30 aliphatic-series oxy-radical of a hydroxyl group, saturation, or partial saturation, or an aryl-low-grade alkyloxy radical. L1 The connection radical chosen from the group which consists of NH-, -O-, and -OCO-Z-NH- (here, Z is C1 - 4 alkylene groups) is expressed. - L2 The connection radical of OCO-Z-CO- and -NHCO-Z-CO- (here, Z is C1 - 4 alkylene groups) is expressed. - R C1 - 30 aliphatic-series radical of a hydrogen atom, saturation, or partial saturation are expressed, and n is the integer of 4-2500. x and y the same -- or -- differing -- those -- the sum total -- two - 300 -- becoming -- an integer -- it is -- and -- x -- and -- y -- having given -- a unit -- those -- a unit -- existing -- a case -- **** -- respectively -- random -- existing -- or -- or -- a block -- forming -- it can exist --] -- expressing -- having -- being according to claim 1 -- preparation -- an approach .
[Claim 3] The preparation approach according to claim 1 or 2 which is what the block copolymer which has a polyoxyethylene segment is expressed with a formula (I), and exists in random, respectively when both the units that x is 0 or attached x and y exist.

[Claim 4] The preparation approach according to claim 1 to 3 chosen from the group which a water poorly soluble drug becomes from KRN5500, taxol, camptothecin, and those water poorly soluble derivatives.
[Claim 5] the following type (I) -- or (II) --
[Formula 2]



(I)

または



(II)

The inside R1 and R3 of [above-mentioned each type expresses a hydrogen atom or a low-grade alkyl group, respectively. R2 expresses C1 - 29 aliphatic-series carbonyl group, or the aryl carbonyl group of a hydrogen atom, saturation, or partial saturation. R4 expresses C1 - 30 aliphatic-series oxy-radical of a hydroxyl group, saturation, or partial saturation, or an aryl-low-grade alkyloxy radical. L1 The connection radical chosen from the group which consists of NH-, -O-, and -OCO-Z-NH- (here, Z is C1 - 4 alkylene groups) is expressed. - L2 The connection radical of OCO-Z-CO- and -NHCO-Z-CO- (here, Z is C1 - 4 alkylene groups) is expressed. - R C1 - 30 aliphatic-series radical of a hydrogen atom, saturation, or partial saturation are expressed, and n is the integer of 4-2500. x and y Are the integer from which it differs and those sum totals are set to 2-300, and the same or the unit which attached x and y When both those units exist, [whether it exists in random, respectively, and] Or it is the drug content polymer micell by which the water poorly soluble drug was enclosed into the polymer micell originating in the block copolymer expressed with] which can form a block and can exist. The polymer micell constituent which comes to contain the drug content polymer micell chosen from the group which a drug becomes from KRN5500, taxol, camptothecin, and those water poorly soluble derivatives coming [the drug content polymer micell which is not condensed mutually substantially].
[Claim 6] The constituent according to claim 5 which is that to which a block copolymer is expressed with a formula (I), and x and y exist in random, respectively.
[Claim 7] The constituent according to claim 5 or 6 whose n a block copolymer is expressed with a formula (I), and L1 in a formula (I) is -NH-, and is the integer of 50-1500 and whose sum total of x and y is the integer of 5-50.

[Translation done.]